Docket No. 17620.105003US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Fumitoshi ASAI	Confirmation No.	8324
Serial No.:	11/520,168	Group Art Unit:	1629
Filed:	September 13, 2006	Examiner:	Finn, Meghan R.
For:	MEDICINAL COMPOSITIONS CONTAINING ASPIRIN		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

I, Paul A. Gurbel, M.D., make oath and declare as follows:

1. I understand that United States Patent Application No. 11/520,168 ("the '168 application"), is a national phase application of International Application No. PCT/JP01/11201 (published as PCT Publication No. WO02/051412), which is jointly owned by DAIICHI SANKYO COMPANY, LIMITED ("Daiichi Sankyo") and UBE INDUSTRIES LTD and that the '168 application is presently pending in the United States Patent and Trademark Office ("USPTO"). I have been asked to express my opinions as to whether it would have been obvious to treat individuals with a combination of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (prasugrel), or a pharmaceutically acceptable salt thereof, and aspirin in view of certain publications relied on by the Examiner at the USPTO. For the reasons explained below, it is my opinion that it would not have been obvious to treat an individual with a combination of prasugrel and aspirin as of December 25, 2000.

Responsive to the Grounds of Rejection in United States Patent Application No. 11/520,168

2. I have been retained by Daiichi Sankyo as a consultant in connection with the '168 patent application and am being paid my customary consultant rate.

3. I have read and understand the specification of the '168 application published as U.S. Patent Application Publication No. 2007/0010499 (Exhibit 1), which is an English translation of International Application No. PCT/JP01/11201. This patent application is directed to various methods of treating an individual with 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, or a pharmaceutically acceptable salt thereof, and aspirin in pharmaceutically effective amounts to treat diseases and/or reduce symptoms associated with thrombus, embolus, stenting, angioplasty, platelet aggregation or thromboembolization.

4. I have reviewed and understand the Office Action dated May 26, 2011 and I understand that the pending claims of the '168 application were rejected by the USPTO. My comments herein are directed to the Examiners rejections under 35 USC §103.

5. I understand that claims have been rejected as anticipated in view of Ogletree et al., U.S. patent 6,509,348, and as obvious in view of Ogletree and Koike et al., U.S. patent 5,288,726. Because I am informed that Applicants have provided evidence to the USPTO that Applicants made their invention prior to the filing date of Ogletree et al., I have focused my analysis on the grounds of rejection which are not based on the Examiner's reliance on Ogletree. Accordingly, my opinions are directed to the non-obviousness of Applicant's claims in view of

Bernat et al., U.S. patent 5,989,578 (Exhibit 2), Asai et al., "CS-747[1], a New Platelet ADP Receptor Antagonist," Annu. Rep. Sankyo Res. Lab., 51: 1-44 (1999)(Exhibit 3) and Koike et al. U.S. patent 5,288,726 (Exhibit 4).

6. I have been advised that under United States patent law, whether the claims of a patent application are obvious is determined based on the level of skill and knowledge of a person of ordinary skill in the art at the time of the invention. It is my understanding that a person of ordinary skill in the art is a hypothetical person having ordinary laboratory skill and a knowledge of relevant and publicly available information in the field of the invention. I have also been advised that the earliest priority date claimed by International Application No. PCT/JP01/11201 is December 25, 2000.

7. I have reviewed Bernat et al., Asai et al., and Koike et al., relied upon by the Examiner. Based on my review, none of these references describe a combination of prasugrel and aspirin.

8. I have also considered how a person of ordinary skill in the art would interpret Bernat et al., Asai et al. and Koike et al. to assess whether the claims of the '168 application are obvious or not. I disagree with the Examiner's rejections for obviousness for at least the reasons that there was insufficient motivation to combine prasugrel and aspirin and that the claimed invention provides numerous unexpected benefits over clopidogrel and aspirin. Since Koike et al. is relied on by the Examiner only in regard to its description of the hydrochloride salt of prasugrel[2] and is only relied on in combination with Bernat et al. and Asai et al., I have provided

[1] Prasugrel was initially referred to as CS-747.
[2] The Examiner improperly cites to compound 252 in Koike et al., as prasugrel; prasugrel is disclosed in Koike et al., as compound 190 at Col. 21, lines 52-54.

my opinions as to why neither Bernat et al., nor Asai et al., alone, or in combination would not make the claims of the '168 patent obvious.

Summary of My Opinions

9. My opinions are summarized as follows:

A. As of December 25, 2000, one skilled in the art would not have had a reasonable expectation that the combination of aspirin and prasugrel would exhibit a clinical benefit that would outweigh the risk of potentially dangerous bleeding;

B. As of December 25, 2000, one skilled in the art would not have reasonably relied on data from ticlopidine or clopidogrel to predict the efficacy or safety of prasugrel in combination with aspirin, because prasugrel has a significantly different chemical structure as compared to clopidogrel and ticlopidine;

C. As of December 25, 2000, a physician had a variety of medications from which to choose in order to inhibit platelet activity and thrombus formation and therefore, would not have necessarily substituted prasugrel in place of either ticlopidine or clopidogrel;

D. The data provided by Table 1 of the specification demonstrate that the combination of prasugrel and aspirin provide a clear synergistic effect against thrombosis *in vivo*, which could not have been expected by one skilled in the art as of December 25, 2000;

E. The combination of prasugrel and aspirin provides superior net clinical benefits over the combination of clopidogrel and aspirin, which could not have been expected by one skilled in the art as of December 25, 2000;

F. The combination of prasugrel and aspirin surprisingly addresses interpatient variability of response to clopidogrel and aspirin, which could not have been expected by one skilled in the art as of December 25, 2000; and

G. The combination of prasugrel and aspirin provides unexpectedly superior results as compared to the combination of clopidogrel and aspirin in patients with diabetes mellitus.

The basis for my opinions and my professional qualifications for stating these opinions are explained below.

My Qualifications

10. I received my M.D. from the University of Maryland School of Medicine in 1983. Subsequently, I completed an internship in 1984 and residency in 1986 in internal medicine at Duke University Medical Center in Durham, North Carolina. Thereafter, I completed a fellowship in pulmonary and critical care at Johns Hopkins University in 1987, followed by fellowships in cardiovascular disease and interventional cardiology at the Duke University Medical Center, where I also served as a chief resident in internal medicine. I am board-certified by the American Board of Internal Medicine in internal medicine with sub-specialty certification in cardiovascular disease and interventional cardiology. I am also a fellow of the American College of Cardiology, American College of Chest Physicians, and the Council on Clinical Cardiology of the American Heart Association. Additionally, I am a member of the Duke University Clinical Cardiology Society.

11. I have been a practicing interventional cardiologist since 1990 and am currently the Director for the Center for Thrombosis Research at Sinai Hospital in Baltimore, Maryland, which has fully equipped state-of-the art laboratories for conducting intricate investigations of

platelet physiology and coagulation. I also currently serve as the Associate Chief for Research of the Department of Medicine and the Director of Therapeutics, Research, and Technology Development for the Cardiac Catheterization Program at Sinai Hospital.

12. The primary areas of my research are related to the anti-platelet agents and the relation of platelet reactivity to ischemic event occurrence. My laboratory was the first to demonstrate the relation between high platelet reactivity to adenosine phosphate (ADP) and ischemic event occurrence in patients undergoing percutaneous coronary intervention (PCI) in Gurbel et al., "Platelet Reactivity in Patients and Recurrent Events Post-Stenting: Results of the PREPARE POST-STENDING Study," J. Am. Coll. of Cardiol., 46:1820-1826 (2005)(Exhibit 5). In particular, my laboratory has been recognized in the field for its studies in antiplatelet drug effects and resistance to antiplatelet drug therapy. Bonello et al., "Census and Future Direction on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate," J. Am. Coll. of Cardiol., 56:919-933 (2010)(Exhibit 6). My laboratory has also amassed one of the largest bodies of data related to platelet inhibition in patients undergoing catheter-based coronary revascularization procedures.

13. In addition to book chapters and monographs, I have authored over 200 articles in the area of interventional cardiology, a majority of which relate to platelet reactivity, in peer-reviewed journals, including leading journals in the field of cardiology such as The American Journal of Cardiology, the Journal of the American Medical Association (JAMA), Platelets, Circulation, and Journal of the American College of Cardiology. I also serve on the editorial boards for Journal of the American College of Cardiology and am a manuscript reviewer for Arteriosclerosis, Thrombosis, and Vascular Biology; American Heart Journal; American Journal of Cardiology; Circulation; Journal of the American College of Cardiology; Lancet; and others.

14. I am also a faculty member in the Cardiology Division of the Johns Hopkins University, which is one of the top 50 U.S. Hospital Heart Programs as rated by the U.S. News and World Report, and am appointed as Associate Professor of Medicine at the Johns Hopkins University School of Medicine in Baltimore, Maryland. I am also a faculty member at the Sinai Hospital in Baltimore, Maryland. My responsibilities in this role include teaching, training and supervising medical residents, who are graduates of medical school, to diagnose and treat patients suffering from cardiovascular disease, including instruction regarding the appropriate use of anti-platelet agents in patients having coronary artery disease, particularly those patients undergoing PCI.

15. I am a citizen of the United State of America. A true and correct copy of my *curriculum vitae* ("CV") is attached as Exhibit 7 to this Declaration.

Platelet Physiology

16. Before explaining the basis for my opinion that the claims of the '168 application are not obvious in view of the prior art, I will briefly provide background on platelet biology and thrombotic disease. Atherothrombosis is the major pathophysiological process responsible for the occurrence of severe ischemic events in patients with cardiovascular diseases. Because cardiovascular disease is a progressive and systemic disease, it was known at the time of the invention that long-term antithrombotic therapies that effectively target the entire arterial vasculature and modulate the key components responsible for thrombus generation are essential to improve patient outcomes.

17. Platelet activation and aggregation play a pivotal role in the generation of occlusive thrombus at the site of coronary arterial plaque rupture. In addition, platelets influence

various endothelial and inflammatory responses during the initiation and progression of atherosclerosis. Under normal conditions, anucleate circulating platelets are in a quiescent state. Healthy vascular endothelium prevents adhesion and activation of platelets by producing antithrombotic factors such as CD39 (ectoADPase), prostaglandin I_2, nitric oxide, heparin, matrix metalloproteinase-9, protein S, and thrombomodulin.

18. Endothelial activation and denudation and frank atherosclerotic plaque rupture expose the subendothelial matrix and release prothrombotic factors during acute coronary syndromes (ACS) and percutaneous interventions. These processes result in localized platelet adhesion and platelet activation. After adhesion to the exposed subendothelial matrix, platelets are activated by shear and the soluble agonists thromboxane A_2 (TxA_2), ADP, and thrombin. These secondary agonists, through an autocrine and paracrine fashion, produce sustained activation of glycoprotein IIb/IIIa receptors, leading to stable platelet-rich thrombus generation.

19. Platelet activation also results in the membrane exposure of phosphatidyl serine, providing binding sites for coagulation factors. The coagulation process results in the generation of thrombin and subsequent platelet-fibrin clot formation. Isoprostanes derived from membrane arachidonic acid through peroxidation have been shown to induce platelet aggregation by activating the receptor for TxA_2. Inhibition of phosphodiesterase and cyclooxygenase (COX) may also play an important role in the treatment of peripheral and cerebrovascular disease.

Opinion A: As of December 25, 2000, one skilled in the art would not have had a reasonable expectation that the combination of aspirin and prasugrel would exhibit a clinical benefit that would outweigh the risk of potentially dangerous bleeding

20. In view of the knowledge and experience with existing anti-thrombotic agents, as of December 25, 2000, one skilled in the art would not have had a reasonable expectation that

the combination of aspirin and prasugrel would exhibit a clinical benefit that would outweigh the risk of potentially dangerous bleeding. This is a threshold issue that relates to the unpredictability of the clinical outcome of the combination of prasugrel and aspirin. As detailed below, my opinion is supported by (1) the adoption of monotherapy in the clinical guidelines setting forth the accepted clinical standard of care at the time of the invention, (2) what was known about prior art anti-platelet agents, particularly thienopyridines and aspirin; and (3) uncertainties regarding combination therapy.

Clinical Standard of Care at the Time of the Invention

21. It is well-known and accepted by clinicians practicing within the field of cardiology that the clinical guidelines published by the American College of Cardiology (ACC) and American Heart Association (AHA) establish the accepted standard of practice for one of ordinary skill in the art. As indicated by the ACC/AHA guidelines around the time of invention, the standard of care at the time of invention was to administer either aspirin or a thienopyridine, but not both.

22. In Braunwald et al., "ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarcation: Executive Summary and Recommendations: Executive Summary and Recommendations, A Report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina)," Circulation, 102:1193-1209 (2000)(Exhibit 8), it was reported that for patients suffering from unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), "[a]ntithrombotic therapy is essential to modify the disease process and its progression to death, MI or recurrent MI." One possible treatment recommendation is antiplatelet or anticoagulation therapy. Specifically, it

was recommended in 2000 that for patients suffering from UA or NSTEMI that "[a]ntiplatelet therapy should be initiated promptly. Aspirin (ASA) is the first choice and is administered as soon as possible after presentation and continued indefinitely." Id. at 1201. Thienopyridines are recommended for individuals who poorly tolerate aspirin, and there is no suggestion that they be combined. Id.

23. Also in Smith et al., "ACC/AHA Guidelines for Percutaneous Coronary Intervention (Revision of the 1993 PTCA Guidelines) -- Executive Summary: A Report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty) Endorsed by the Society for Cardiac Angiography and Interventions," Circulation, 103:3019-3041 (2001)(Exhibit 9), it was reported that for patients undergoing PCI, "[a]spirin reduces the frequency of ischemic complications after coronary angioplasty." Id. at 3038.

24. Furthermore, in Smith et al., "AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology," J. Am. Coll. Cardiol., 38: 1581-1583 (2001)(Exhibit 10), one of the recommended ways to aggressively reduce risk of patients with atherosclerotic cardiovascular disease is to administer antiplatelet agents or anticoagulants, which is to "[s]tart and continue indefinitely aspirin 75 to 325 mg/d if not contraindicated." Id. at 1582. Again, there is no suggestion of combining aspirin with a thienopyridine.

25. Even in 2001, after the earliest priority date of the '168 application, the standard of care, as established by the well-accepted guidelines, recommended administration of aspirin or a thienopyridine, but not in combination. The guidelines for PCI also refer to thienopyridines as

"alternative antiplatelet agents in aspirin-sensitive patients during coronary angioplasty." Smith et al., at 3038. The guidelines for treating patients with atherosclerotic cardiovascular disease also recognized thienopyridines as alternatives, and not adjuncts, to aspirin and specifically recommended that one skilled in the art should "[c]onsider clopidogrel 75 mg/d or warfarin if aspirin is contraindicated." Smith et al., at 1582.

26. As of the earliest priority date for the '168 application, December 25, 2000, the only combination of antithrombotic agents recommended by the guidelines at that time was a combination of aspirin, unfractionated heparin, and a platelet GP IIb/IIIa receptor antagonist, which was reported to be "the most effective therapy." Id. at 1201.

Risks of Administering Aspirin

27. Aspirin mediates its antiplatelet effects by inhibiting the COX-1 enzyme. See Vane et al., "Cyclooxygenases 1 and 2," Annu. Rev. Pharmacol. Toxicol., 38:97-120 (1998)(Exhibit 11). The antiplatelet effect of aspirin was reported at that time as being attributed primarily to the irreversible inhibition of platelet COX-1 by acetylation of serine residue 530, resulting in a downstream reduction in the synthesis of TxA_2 and consequent TxA_2-induced platelet activation/aggregation. See Awtry and Loscalzo, "Aspirin," Circulation, 101: 1206-1218 (2000)(Exhibit 12). In addition, aspirin is known to reduce thrombin generation, to enhance fibrin clot permeability and clot lysis, and to promote nitric oxide production in platelets. Aspirin also has anti-inflammatory properties that may enhance its antithrombotic effect. See Id.

28. Despite the usefulness of aspirin as a therapeutic agent, it was known before the earliest priority date of the '168 application, that there are a number of contraindications associated with aspirin that rendered it unsuitable under certain circumstances; "these are intolerances and allergy (primarily manifested as asthma), active bleeding, hemophilia, active

retinal bleeding, severe untreated hypertension, an active peptic ulcer, or another serious source of gastrointestinal or genitourinary bleeding." Braunwald et al. at 1201.

29. A review paper published in 2000, Awtry and Loscalzo, "Aspirin," Circulation, 101:1206-1218 (2000) provides a summary of various adverse effects associated with aspirin observed across numerous clinical trials. Awtry and Loscalzo report that "[t]he inhibition of prostaglandin synthesis is responsible for the anti-inflammatory effects of aspirin but also results in the alteration of normally protective prostaglandin functions with potentially serious consequences, including gastric ulcers, renal failure and impaired platelet function with resultant hemorrhagic complications." Id. at 1211. As further explained by Awtry and Loscalzo, aspirin-induced inhibition of COX "likely accounts in part for the more frequent development of GI side effects in the aspirin-treated in most trials." Id. at 1211. Based on the published clinical information available at the time of invention, Awtry and Loscalzo report that:

> In the United Kingdom Transient Ischaemic Attack (UK-TIA) trial, the incidence of GI symptoms was not only significantly higher in the aspirin-treated group than in the placebo group, but GI symptoms were significantly more frequent in the high-dose (1200 mg/d) than in the low-dose (300 mg/d) aspirin groups ($2P <$ 0.001 for both comparisons). An overview of randomized trials of aspirin therapy similarly found that GI toxicity (both major and minor was dose related with daily doses between 30 and 1300 mg). Nonetheless, even low doses of aspirin (50 to 75 mg/d) are not free from side effects with increased GI bleeding, and frequently precipitate the discontinuation of therapy.

Id. at 1211. Additionally, Awtry and Loscalzo report that:

> Several studies have suggested an increase in the risk of hemorrhagic stroke in patients treated with aspirin in the setting of an AMI or acute ischemic strike, as well as when aspirin is used for the primary or secondary prevention of cardiovascular events. A recent meta-analysis of 16 trials comprising 55 462 patients treated with aspirin or control therapy demonstrated a significant increase in hemorrhagic strokes (RR 1.84; $P < 0.001$) despite a decrease in ischemic strokes, total strokes, and MI. This relative

> risk translated into an absolute increase of 12 hemorrhagic strokes per 10 000 patients treated with aspirin.

Id. at 1212. Awtry and Loscalzo also report that administration of aspirin to patients suffering from aspirin intolerance or sensitivity "results in the development of bronchoconstriction, rhinitis, and/or urticaria." Id. at 1212.

30. It was understood by those skilled in the art around 2000 that alternatives to regular aspirin were needed to reduce these side-effects. As reported in Awtry and Loscalzo, "[a]ttempts have been made to decrease the gastric toxicity of aspirin by pharmacological manipulation." Id. at 1212. One possible strategy reported by Awtry and Loscalzo was to "preferentially inhibit COX-2 and allow for the inhibition of inflammatory prostaglandins while leaving the homeostatic prostaglandins relatively intact." An alterative strategy reported by Awtry and Loscalzo was to decrease the risk of gastric ulceration, erosion and hemorrhage, by "coadministration of aspirin with the synthetic PGE_2 analog misoprostol [which was reported to allow] for the complete inhibition of TXA_2 synthesis in platelets while maintaining gastric protection." Id. at 1213.

31. In view of the risks associated with inhibition of the COX-1 enzyme by aspirin, each of the three guidelines from at or around the time of invention recommended that thienopyridines be administered as alternatives to, and not adjuncts with, aspirin. In particular, the well-accepted guidelines for UA or NSTEMI patients at the time of invention recommended that "[a] thienopyridine (clopidogrel or ticlopidine) should be administered to patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance." Braunwald et al. at 1201. Specifically, the guidelines reported that clopidogrel and ticlopidine "are indicated in patients with UA/NSTEMI who are unable to tolerate ASA due to either

hypersensitivity or major gastrointestinal contraindications -- principally recent significant bleeding from a peptic ulcer or gastritis." Id. at 1201.

Risks Known in 2000 About Ticlopidine and Clopidogrel

32. In addition to the known risks of aspirin, risks, particularly for bleeding, were known for ticlopidine and clopidogrel. In particular, Asai et al., cited by the Examiner comments on the use of ticlopidine and clopidogrel, which had been shown to inhibition of ADP induced aggregation and were approved in the U.S. at the time of the invention for use as antiplatelet agents. Ticlopidine was the first ADP inhibitor approved for use as antiplatelet therapy. However, as reported in Asai et al., "[t]icolopidine can have significant adverse effects at common dosage levels... because 1% of patients receiving ticlopidine may experience severe agranulocytosis." Asai et al. at 3. As reported in Moussa et al., "Effectiveness of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin in Preventing Stent Thrombosis After Coronary Stent Implantation" Circulation, 99:2364-2366 (1999) (Exhibit 13):

> The incidence of neutropenia with ticlopidine is proportional to the duration of treatment (up to 2.4%), and it may resolve with drug cessation in most but not all cases. Another serious side effect of ticlopidine is thrombotic thrombocytopenic purpura (TTP). A recent review documented 60 cases of TTP among patients treated with ticlopidine, with an associated mortality rate of 33%. In this review, 12 patients developed TTP after receiving ticlopidine for ≤3 weeks after stent implantation. Other common but less morbid adverse effects reported to accompany ticlopidine use are gastrointestinal symptoms.

Moussa et al. at 2365.

33. Clopidogrel was subsequently introduced as an antiplatelet agent because "clopidogrel has a favorable safety profile compared with ticlopidine, for which routine hematological monitoring is mandatory to ensure early detection of potentially lethal

hematological events." Id. at 2365. However, the publications noted concerns relating to the risk/benefit of clopidogrel and ticlopidine.

34. As reported in Asai et al., "the clinical efficacy of clopdiogrel over aspirin has proven just marginal." The effect of clopidogrel as compared to aspirin was reported in the CAPRIE trial, which was the largest clinical trial involving clopidogrel known at the time of the invention published in 1996 by the CAPRIE Steering Committee, "A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE)," Lancet, 348: 1329-39 (1996)(Exhibit 14). The CAPRIE trial was designed "to assess the potential benefit of clopidogrel, compared with aspirin, in reducing the risk of ischaemic stroke, myocardial infarction, or vascular death in patients with recent ischaemic stoke, recent myocardial infarction, or peripheral arterial disease." Id. at 1330. As reported in the CAPRIE trial:

> The primary analysis of efficacy was by intention-to-treat and based in the incidence of the first occurrence of ischaemic stroke, myocardial infarction, or vascular death among all patients randomised. There were 939 events in the clopidogrel group during 17 636 patient-years at risk, an average rate per year of 5.32%. There were 1021 events in the aspiring group during 17 519 patient-years at risk, an average rate per year of 5.83%.

Id. at 1333. The CAPRIE trial also reported that there was a "lack of observed benefit of clopidogrel over aspirin in the myocardial infarction subgroup" and there was evidence of "possible heterogeneity of treatment among the clinical subgroups." Id. at 1335. Specifically, the CAPRIE trial reported that "[f]or patients with myocardial infarction, the average event rate per year was 5.03% in the clopidogrel group compared with 4.84% in the aspirin group: a relative-risk increase of 3.7% (22.1 to -12.0) associated with clopidogrel (p = 0.66)." Id. at 1334.

35. The CAPRIE trial also recognized that "[b]leeding is a complication of antiplatelet treatment." Id. at 1336. The CAPRIE trial reported that:

> severe bleeding was more common with aspirin, with the difference in severe gastrointestinal bleeding being statistically significant. Non-fatal primary intracanial haemorrhage and haemorrahgic deaths were predefined outcome events that could possibly be caused by study drug. These were less frequent in the clopidogrel group (0.39%) than in the aspirin group (0.53%).

Id. at 1336.

36. The risk of bleeding associated with clopidogrel was also recognized in the regulatory documents in the U.S. and EMEA for PLAVIX, the commercially available pharmaceutical product containing clopidogrel as its active ingredient, and the safety of co-administration of clopidogrel and aspirin was not known. As stated by the November 17, 1997 version of the Package Insert for PLAVIX that accompanied the product's initial approval in the United States (Exhibit 15):

> PLAVIX prolongs the bleeding time. In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. PLAVIX should be used with caution in patients who have lesions with a propensity of bleed (such as ulcers). Drugs that might induce such lesions (such as aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]) should be used with caution in patients taking PLAVIX.

Package Insert for PLAVIX at 8. Similarly in a revised European Public Assessment Report (EPAR) report dated October 2000 (Exhibit 16), it was reported that **aspirin is not recommended with Plavix**. See EPAR Report for PLAVIX at 3 (October 2000), emphasis added.

Uncertainties Regarding the Net Benefit of Combination Therapy

37. In 2000, it was still not known whether the combined administration of a thienopyridine (e.g., ticlopidine or clopidogrel) and aspirin provided a clinical benefit over aspirin alone since, for example, it was unknown whether co-administration of a thienopyridine (e.g., ticlopidine or clopidogrel) and aspirin would provide sufficient benefits to outweigh the

potential bleeding risks compared to administration of the thienopyridine (e.g., ticlopidine or clopidogrel) alone.

38. By 2000, there had been reports of co-administration of ticlopidine with aspirin as well as clopidogrel plus aspirin. With respect to preventing stent thrombosis after coronary stent implantation, Moussa et al., which was published in 1999, reported that "[t]he combination of ticlopidine and aspirin has been confirmed to be superior to aspirin alone or aspirin and coumarin in randomized trials." Id. at 2364. Moussa et al. cites two publications as the basis for this statement, one of which is Leon et al., "A Clinical Trial Comparing Three Antithrombotic-Drug Regiments After Coronary-Artery Stenting," N. Engl. J. Med., 339: 1665-71 (1998)(Exhibit 17). Leon et al. report that "[t]he chief finding [of its study] was that a combination of aspirin and ticlopidine was superior to either a combination of warfarin and aspirin or aspirin alone in the prevention of stent thrombosis after successful stenting." Id. at 1669. However, Leon et al. goes on to state that:

> The significantly lower incidence of stent thrombosis during treatment with aspirin and ticlopidine as compared with treatment with aspirin alone was offset by a slight but significantly increased risk of hemorrhagic and vascular surgical complications. Despite the widespread belief that combination therapy with aspirin and ticlopidine is associated with a lower rate of vascular surgical complications than therapy with aspirin and warfarin, there was no significant difference in these end points between the two groups.

Id. at 1669.

39. In addition, the November 17, 1997 version of the Package Insert for PLAVIX acknowledged that "[t]he safety of chronic concomitant administration of aspirin and PLAVIX has not been established." Package Insert for PLAVIX at 9.

40. In 2000, the CLASSICS trial studied "the safety of clopidogrel (with or without a loading dose) in combination with aspirin compared with ticlopidine in combination with aspirin

in patients who had undergone successful coronary stenting." Bertrand et al., "Double-Blind Study of the Safety of Clopidogrel With and Without a Loading Dose in Combination With Aspirin Compared with Ticlopidine in Combination With Aspirin After Coronary Stenting: The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)," Circulation, 102: 624-629, 625 (2000)(Exhibit 18). The CLASSICS trial reported that clopidogrel demonstrates "a superior safety profile" based on a composite evaluation of the primary end points consisting of major peripheral or bleeding complications, neutropenia, thrombocytopenia or early discontinuation of the study drug for noncardiac adverse events. See Id. at 628. However, the data from the CLASSICS trial show that the combination of clopidogrel and aspirin was not associated with less hemorrhagic risk than ticlopidine and aspirin. Rather, the CLASSICS trial reports that "[t]he incidence of major peripheral or bleeding complications was low and similar in the 3 groups (1.2% for ticlopidine, 1.2% for 75 mg QD clopidogrel, and 1.5% for clopidogrel loading dose during the treatment period)." Id. at 627.

41. As reported in a paper describing the design of the CURE trial published before the earliest priority date of the '168 application, "[t]he Clopidogrel in Unstable Angina Recurrent Events (CURE) trial was designed to test the hypothesis that treatment with the combination of clopidogrel and aspirin is superior to aspirin alone when initiated early and continued long-term, in the prevention of major cardiovascular events in patients with acute coronary syndrome." CURE Study Investigator, "The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme, rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease," European Heart Journal, 21: 2033-2041, 2034 (2000)(Exhibit 19). Thus, an entire clinical study was commenced in 2000, the same year as Applicants' priority date, directed at assessing whether the combination of aspirin and

clopidogrel provided a benefit over aspirin alone in patients, because whether or not such benefits would manifest in patients was at that time still unknown.

42. Results of this clinical trial were not reported until 2001, after the earliest priority date of the '168 application. See "The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigator: Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation," N. Engl. J. Med., 345(7) 494-502 (August 16, 2001)(Exhibit 20).

43. Thus, as of December 25, 2000, the art recognized significant potential risks associated with administration of a thienopyridine, such as ticlopidine or clopidogrel, with aspirin, and could not have predicted whether the potential benefits provided by such a combination would outweigh the potential risks.

Risks Known in 2000 About Prasugrel

44. Based upon what was known about prasugrel as of the earliest priority date of the '168 application, one skilled in the art would not have known that adding aspirin to prasugrel would have provided any additional anti-thrombotic effect or increased the net clinical benefit. At the time of the invention, prasugrel was a nascent pharmaceutical active agent undergoing preliminary animal studies and Phase I clinical trials (*i.e.*, preliminary studies to demonstrate that the compound is safe for use in humans)(see Sugidachi et al., "The *in vivo* pharmacological profile of CS-747, a novel antiplatelet agents with platelet ADP receptor antagonist properties," British Journal of Pharmacology, 129: 1439-1446 (2000)(Exhibit 21) and was not yet approved for clinical use. Based on a study in which the active ingredients were orally administered to SD rats once a day for 3 days, Asai et al. reported that "[c]lopidogrel (3-30 mg/kg/day, *p.o.*) also

inhibited platelet aggregation, but the effect of clopidogrel was 10-fold less potent than that of CS-747." Id. at 11. Additionally, comparing the bleeding time after administration in SD rats, Asai et al. reported that CS-747 was "the most potent in the prolongation of bleeding time" as compared to clopidogrel and ticlopidine. Id. at 16. As shown in Table 1 of Sugidachi et al., the BT_2 dose, which is the dose at which the agents double the control bleeding time, for CS-747 was 0.50 mg/kg. The BT_2 dose for CS-747 is significantly lower than that for clopidogrel (which has a BT_2 of 4.6 mg/kg) and ticlopidine (which has a BT_2 of 130 mg/kg).

45. At the end of 1999, Asai et al. reported "[t]hree studies in Phase I: single-dose, multiple-dose, and food-effect studies of CS-747... to characterize the pharmacodynamics, pharmacokinetics, and safety features of CS-747, after single and multiple oral administration in healthy Caucasian male volunteers." Id. at 35. More particularly, Asai et al. reported that "CS-747 was demonstrated to have a potent and long-lasting inhibitory activity on *ex vivo* platelet aggregation in healthy Caucasian male volunteers, without any serious adverse events." Id. at 42. However, Asai et al. also reported a prolongation of bleeding time in healthy volunteers even after a single dose of CS-747. The data provided in Asai et al. demonstrated that the maximal prolongation of bleeding for CS-747 was slightly less than 6 times the baseline values. See Id. at 42.

46. In 2000, prasugrel was known to be a potent inhibitor of ADP-induced platelet aggregation, more potent, in fact, than ticlopidine or clopidogrel. And, specifically, prasugrel had been shown to be a potent and specific inhibitor of the receptor $P2YT_{ac}$ (now known as the $P2Y_{12}$ receptor). See, Sugidachi et al. and Asai et al. Studies prior to December 2000 indicate that inhibition of signaling via the $P2Y_{12}$ receptor can also block signaling though the thromboxane A_2 (TXA_2) pathway, which is the pathway through which aspirin acts. See Storey,

"The central role of the P_{2T} receptor in amplification of human platelet activation, aggregation, secretion and procoagulant activity," Brit. J. Haem. 110:925-934 (2000)(Exhibit 22); and Paul et al., "Molecular Mechanism of Thromboxane A_2-induced Platelet Aggregation: Essential Role for $P2T_{AC}$ and α_{2A} Receptors," J. Biol. Chem. 274:29108-29114 (1999)(Exhibit 23).

47. In view of the understanding in 2000 of the receptor signaling involved in platelet aggregation and the potency of prasugrel to block $P2Y_{12}$ signaling, one skilled in the art would have doubted whether adding aspirin to prasugrel would have significantly increased its anti-thrombotic effects. And, because of the known risks of aspirin, one skilled in the art could not have predicted whether the clinical benefit, if any, of adding aspirin to prasugrel would have outweighed the added risks associated with aspirin therapy.

48. Therefore, had it been available for therapeutic use, one skilled in the art would have administered prasugrel alone because there was no information at the time regarding the benefit of adding aspirin to prasugrel therapy, and in fact, there was reason to doubt that aspirin would have added to the clinical benefit of prasugrel at that time. It was unknown whether prasugrel and aspirin would provide a sufficient net clinical benefit over prasugrel alone or over aspirin alone and the risk of bleeding with prasugrel and aspirin at that time was entirely unknown.

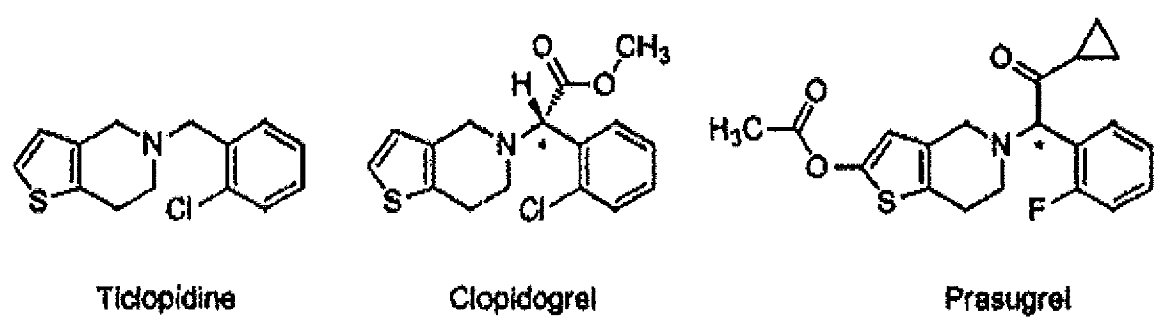
49. Furthermore, because prasugrel was known as of December 2000 to be so much more potent than clopidogrel and that significant antiplatelet responses could be achieved with lower doses of prasugrel than clopdiogrel, one skilled in the art would not have expected the addition of aspirin to be necessary to achieve the same level of therapeutic benefit as that achieved by clopidogrel and aspirin. Rather, one skilled in the art would have been motivated to

use prasugrel alone, so as to avoid the potential risks associated with aspirin, particularly the significant GI risks associated with aspirin.

Opinion B: As of December 25, 2000, one skilled in the art would not have reasonably relied on data from ticlopidine or clopidogrel to predict the efficacy or safety of prasugrel in combination with aspirin, because prasugrel has a significantly different chemical structure as compared to clopidogrel and ticlopidine

50. It is my opinion that as of December 25, 2000, one skilled in the art would not have reasonably relied on data from administration of ticlopidine or clopidogrel to predict the efficacy or safety of prasugrel in combination with aspirin, because prasugrel has a significantly different chemical structure as compared to clopidogrel and ticlopidine which difference in chemical structure manifests as a significantly more potent drug than either ticlopidine or clopidogrel. The basis of my opinion is detailed below.

51. Although ticlopidine, clopidogrel and prasugrel are all thienopyridine derivatives, the chemical structure of prasugrel is significantly different from that of ticlopidine and clopidogrel. The chemical structure of ticlopidine, clopidogrel and prasgurel are shown below:



(* marks represent asymmetric carbon)

As can be seen from the above, these three thienopyridines share the same ring structure, but prasugrel has different side chains:

- Ticlopidine and clopidogrel both have a chlorine substituent on the phenyl group; however, the chlorine substituent which ticlopidine and clopidogrel have in common is replaced by a fluorine atom in prasugrel.
- Compared to ticlopidine, clopidogrel has an additional methyl ester group attached to the carbon atom connecting the thienopyridine and phenyl ring structures. Addition of this substituent makes the carbon atom a chiral center, which allows for R and S stereoisomers. The same chiral center can be seen in the structure of prasgurel; however, instead of the methyl ester group, the chiral carbon of prasugrel is substituted with substantially different functional group, a cyclopropyl ketone group.
- In addition, the thiophene ring of prasugrel is further substituted with an acetyloxy group.

52. In considering a pharmaceutical product, it is my opinion that one skilled in the art would understand that changes to the chemical structure of a compound provide for very different molecular size, shape, and charge interactions and could potentially lead to very different safety and efficacy effects. For example, comparing ticlopidine to clopidogrel, the addition of a single methyl ester group drastically increased the potency and safety of clopidogrel. In addition the differences in structure between clopidogrel and prasugrel result in different metabolic fates of clopidogrel and prasugrel and prasugrel's ten (10) fold greater potency than clopidogrel.

53. At the end of 2000, there was no predictable connection between a thienopyridine structure and antiplatelet activity.

54. Therefore, in view of the multiplicity of substitutions necessary to modify either ticlopidine or clopidogrel to obtain the chemical structure of prasugrel, it is my opinion that one

skilled in the art would not have had any reasonable expectation of an acceptable efficacy to safety ratio of prasugrel in combination with aspirin, without having conducted an experiment based on this specific combination.

Opinion C: As of December 25, 2000, a physician had a variety of medications from which to choose in order to inhibit platelet activity and thrombus formation and therefore, would not have necessarily substituted prasugrel in place of either ticlopidine or clopidogrel

55. It is my opinion that as of December 25, 2000, a physician had a variety of medications from which to choose in order to inhibit platelet activity and thrombus formation and therefore, would not have necessarily substituted prasugrel in place of either ticlopidine or clopidogrel. As detailed below, my opinion is supported by the numerous different anti-thrombotic therapies known as of December 2000.

56. Relying on Bernat et al., in combination with Asai et al., the Examiner states: "it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute prasugrel for clopidogrel or ticlopidine in Bernat et al., because it was more potent and less toxic. There is a reasonable expectation of success because both prasugrel and aspirin are known to be effective anti-platelet agents and synergism between aspirin and prasugrel would be expected based on the synergism established between clopidogrel or ticlopidine and aspirin." Office Action at 13. Besides the uncertainty regarding the potential risks of combing prasugrel and aspirin as discussed above, there were many other alternatives besides prasugrel that may have been considered by one skilled in the art. As of December 2000, there were numerous different therapies that were known to have anti-thrombotic effects. These anti-thrombotic agents include: agents that inhibit platelet activation/aggregation ("antiplatelet agents"), agents

that inhibit the coagulation system ("anticoagulants"), and agents that dissolve pre-formed thrombi ("thrombolytics").

57. As of December 2000, numerous approaches were being investigated to identify efficacious agents that would control platelet activation/aggregation and the coagulation cascade as well as dissolution of pre-formed thrombi to ultimately prevent or treat diseases caused by thrombus or embolus. A brief list of the different classes of agents and several representative examples from each class having been pursued is given below. See Verstraete, M., *et al.* (Eds.) Cardiovascular Thrombosis: Thrombocardiology and Thromboneurology, Lippincott Williams and Wilkins, Second Edition, 1998, Chapters 9-11, and 14 (Exhibit 24); in Ferguson III, JA, *et al.* (Eds.) Antiplatelet Therapy in Clinical Practice, Martin Dunitz Press, 2000, Chapters 6 and 8-11 (Exhibit 25).

Antiplatelet agents available and under investigation:

- COX inhibitors: e.g., aspirin and novel formulations thereof
- Adenosine diphsophate (ADP) receptor antagonist: e.g., ticlopidine, clopidogrel, AR-C69931 MX, prasugrel
- Thromboxane receptor antagonists (TRA): e.g., Sulotraban, SQ30741
- Thromboxane synthase inhibitors (TSI): e.g., Dazoxiban, pirmagrel
- Combined TRA/TSI: e.g. Ridogrel
- Glycoprotein IIb-IIIa antagonists (iv): e.g., abciximab, epitifibatide, tirofiban, lamifiban
- Glycoprotein IIb-IIIa antagonists (oral): e.g., Xemlofiban, orbofiban, roxifiban
- Phosphodiesterase inhibitors: e.g., dipyridamole, cilostazol
- Serotonin receptor antagonists: e.g., Ketanserin
- Nitric oxide analogues, promoters: e.g., L-arginine, Prolino/NO, NONOates
- Protacyclin and PGE1 analogues: e.g., ilosprost, beraprost, ciprostene
- vWF inhibitors: e.g., monoclonal antibodies, aurintricarboxylic acid

Anticoagulants:

- Heparinoids: e.g., Unfractionated heparin, LMWH (e.g. Enoxaparin and Dalteparin) pentasaccharides
- Factor Xa inhibitors: e.g., DX-9065a
- Factor IIa (thrombin) inhibitors: e.g., Hirudins, bivalirudin, argatroban
- Tissue factor modulators: e.g., TFPI
- Coumarins: e.g., Coumadin and analogues
- Dextran

Thrombolytics

- Plasminogen activators: e.g., t-PA, TNK-tPA, streptokinase, urokinase/analogues staphylokinase

58. The Examiner appears to substitute prasugrel in place of either ticlopidine or clopidogrel in combination treatments with aspirin, as described in Bernat et al., and Asai et al.. However, as shown above, one skilled in the art would have had a large number of potential antithromotic agents from which to choose and would not have necessarily substituted prasugrel in place of either ticlopidine or clopidogrel.

Opinion D: The data provided by Table 1 of the specification demonstrate that the combination of prasugrel and aspirin provide a clear synergistic effect against thrombosis in vivo, which could not have been expected by one skilled in the art as of December 25, 2000

59. As explained below, it is my opinion that the data provided by Table 1 of the specification demonstrate that the combination of prasugrel and aspirin provide a clear synergistic effect against thrombosis *in vivo*, which could not have been expected by one skilled in the art as of December 25, 2000.

60. The specification of the '168 application provides data demonstrating that the combination of prasugrel and aspirin provides an unexpected synergistic effect against

thrombosis *in vivo*. The data provided in Table 1 on page 13 of the specification is reproduced below:

Compounds		Thrombus Weight (mg)	Inhibition Rate (%)
Compound A (mg/kg)	Aspirin (mg/kg)		
0	0	52.3 ± 1.2	----
0	10	46.6 ± 2.8	12.3 ± 4.44
0.3	0	43.5 ± 2.1	17.0 ± 4.1
0.6	0	37.5 ± 2.1	28.3 ± 4.0
0.3	10	30.5 ± 3.5	41.8 ± 6.6
0.6	10	23.2 ± 3.8	55.7 ± 7.2

As can be seen in Table 1 of the specification, 10 mg/kg of aspirin provides an inhibition rate of 12.3 ± 4.44 %, whereas 0.3 mg/kg of prasugrel provides an inhibition rate of 17.0 ± 4.1 % and 0.6 mg/kg of prasugrel provides an inhibition rate of 28.3 ± 4.0 %. The combined administration of 0.3 mg/kg of prasugrel with 10 mg/kg was shown to provide an inhibition rate of 41.8 ± 6.6 %, which is greater than the sum of the rates of inhibition for each of the components. Similarly, the combined administration of 0.6 mg/kg of prasugrel with 10 mg/kg was shown to provide an inhibition rate of 55.7 ± 7.2 %, which is greater than the sum of the rates of inhibition for each of the components.

Opinion E: The combination of prasugrel and aspirin provides superior net clinical benefits over the combination of clopidogrel and aspirin, which could not have been expected by one skilled in the art as of December 25, 2000

61. It is my opinion that, the combination of prasugrel and aspirin provides superior net clinical benefits over the combination of clopidogrel and aspirin, which could not have been

expected by one skilled in the art as of December 25, 2000. Specifically, bleed risks for antiplatelet therapy, particularly for prasugrel and for aspirin, were of concern to those skilled in the art as of the priority date. In fact, based on animal studies, Asai et al. reported that "CS-747 was the most potent in the prolongation of bleeding time," but Asai et al. concluded from these studies that "CS-747 and clopidogrel may comparatively have similar ratios of benefit/bleeding risk." Id. at 16. Therefore, one skilled in the art would not have had any expectation that the combination of prasugrel and aspirin would provide clinical benefits that would outweigh the bleeding risks associated with administration of both prasugrel and aspirin. As detailed below, my opinion is supported by clinical data demonstrating that the clinical benefits of the combination of prasugrel and aspirin significantly outweigh the bleeding risks associated with administration of both prasugrel and aspirin.

62. For example, the TRITON-TIMI 38 trial, reported in Wiviott et al., "Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes," N. Engl. J. Med., 357:20, 2001-15 (2007)("2007 Wiviott")(Exhibit 26), provides data demonstrating that administration of prasugrel in combination with aspirin results in statistically significant reductions in the incidence of most major end points listed as compared to clopidogrel and aspirin. The TRITON-TIMI 38 trial was a large scale clinical study conducted with 13,608 patients with acute coronary syndromes with scheduled PCI from 707 sites in 30 countries. Id. at 2002-3. Patients were administered with either a 60 mg loading dose of prasugrel or 300 mg loading dose of clopidogrel and maintenance doses of either 10 mg of prasugrel or 75 mg of clopidogrel, respectively. Use of aspirin was a requirement with all patients. Id. Table 2 of the 2007 Wiviott paper, which provides clinical data showing improvements for the combination of prasugrel and aspirin over clopidogrel and aspirin are reproduced below:

Table 2. Major Efficacy End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6813)	Clopidogrel (N=6795)	Hazard Ratio for Prasugrel (95% CI)	P Value†
	no. of patients (%)			
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	0.89 (0.70–1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78–1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73–0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75–0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54–0.81)	<0.001
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76–0.92)	<0.001
Stent thrombosis‡	68 (1.1)	142 (2.4)	0.48 (0.36–0.64)	<0.001

* The percentages are Kaplan–Meier estimates of the rate of the end point at 15 months. Patients could have had more than one type of end point. Death from cardiovascular causes and fatal bleeding (Table 3) are not mutually exclusive, since intracranial hemorrhage and death after cardiovascular procedures that were complicated by fatal bleeding were included in both end points. MI denotes myocardial infarction.

† P values were calculated with the use of the log-rank test. The prespecified analysis for the primary end point used the Gehan–Wilcoxon test, for which the P value was less than 0.001.

‡ Stent thrombosis was defined as definite or probable thrombosis, according to the Academic Research Consortium; the numbers of patients at risk were all patients whose index procedure included at least one intracoronary stent: 6422 patients in each of the two treatment groups.

Based on the data shown above, the 2007 Wiviott paper reports that the combination of prasugrel and aspirin as compared to clopidiogrel and aspirin resulted in:

- a 2.2% absolute reduction and a **<u>19%</u> relative reduction** in the rate of the primary efficacy end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke);
- a 2.3% absolute reduction and a **<u>24%</u> relative reduction** for myocardial infarction (MI);
- a 1.2% absolute reduction and a **<u>34%</u> relative reduction** for urgent target-vessel revascularization;

- a 1.3% absolute reduction and a **<u>52%</u> relative reduction** for stent thrombosis; and
- a 0.3% absolute reduction and a **<u>42%</u> relative reduction** for recurrent myocardial infarction followed by death from cardiovascular disease. <u>Id.</u> at 2008.

63. As further evidence of the superior clinical benefits provided by the administration of a combination of prasugrel and aspirin as compared to combination of clopidogrel and aspirin, Smith et al., "Mortality Benefit with Prasugrel in TRITON-TIMI 38 Coronary Artery Bypass Grafting (CABG) Cohort: Risk Adjusted Retrospective Data Analysis," <u>Circulation</u> 122, A10881 (2010)(Exhibit 27) reports that "[a] significantly lower mortality was observed in the PRAS cohort… [and o]verall all-cause mortality was 2.31% in the PRAS cohort compared to 8.67% in the CLOP cohort, with a hazard ratio of 0.26 (Log-rank p=0.016)."

64. In contrast, it was reported in the CHARISMA trial, that "[o]verall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes." Bhatt et al., "Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events," <u>N. Engl. J. Med.</u>, 354: 1706-17 (2006)(Exhibit 28). It is important to note that the CHARISMA trial was a large scale clinical trial in a broad population of patients and was designed to "test the hypothesis that long-term treatment with a combination of clopidogrel plus aspirin may provide greater protection against cardiovascular events than aspirin alone in a broad population of patients at risk." <u>Id.</u> at 1707.

65. Taken as a whole, the data demonstrate that the combination of prasugrel and aspirin surprisingly provides greater net clinical efficacy than clopidogrel and aspirin for a number of endpoints including reducing the number of patients who suffer from significant adverse events. In 2000, it was entirely unknown whether prasugrel and aspirin combination

therapy would be associated with a prohibitive bleeding risk. Such important and unexpected results were clearly not predictable at the priority date of the '168 application providing additional evidence that the claims are not obvious.

66. Additionally and critically, not only does the claimed invention provide an unexpectedly superior clinical benefit as compared to the combination of clopidogrel and aspirin, adverse bleeding events, which would have been expected as of the priority date to occur with the combination of prasugrel and aspirin, do not actually outweigh the anti-thrombotic benefits of prasugrel and aspirin. Thus, the claimed combination is not obvious because it provides a greater net clinical benefit, *i.e.*, a superior therapeutic benefit as compared to the risk of adverse bleeding events than would have been expected at the priority date.

67. Complicating the identification of more efficacious treatments for disease associated with platelet thrombus and embolism formation was finding drugs that exhibited the appropriate balance between sufficiently inhibiting platelet aggregation without causing an unacceptable bleeding risk. As discussed above, as of the priority date, the art recognized that administration of thienopyridines carried a significant bleeding risk. Due to its greater potency as compared to ticlopidine and clopidogrel, one would have expected a potential increased risk to be associated with prasugrel, particularly when combined with aspirin which has its own, additional GI and bleeding risks. In view of these anticipated risks, one skilled in the art would not reasonably have expected that the clinical benefits of the combination of prasugrel and aspirin would outweigh the bleeding risk when administered to patients. In fact, clinical data demonstrate that the clinical benefits of the combination of prasugrel and aspirin do outweigh the risks.

68. The TRITON-TIMI 38 trial described by the 2007 Wiviott paper demonstrates that in a large majority of patients, without prior history of stroke or transient ischemic attack and being less than 75 years old and having a body weight greater than 60 kg, "had a significant net clinical benefit with the prasugrel [and aspirin] regimen studied, as compared with the clopidogrel [and aspirin] regimen (hazard ratio 0.80; 95% CI, 071 to 0.89; P<0.001). As can be seen in Table 4 of the 2007 Wiviott paper, when balancing the efficacy and safety of prasugrel in combination with aspirin, patients without the above listed risk factors showed a hazard ratio of less than 1 for (1) death from cardiovascular causes, nonfatal MI, or nonfatal stroke and (2) death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding. Contrary to the statement reported in Asai that "CS-747 and clopidogrel may comparatively have similar ratios of benefit/bleeding risk," the large scale clinical data from the TRITON-TIMI 38 trial suggest that prasugrel in combination with aspirin **surprisingly provides more benefit than bleed risk** for the majority of patients as compared to clopidogrel and aspirin. Cf. Asai, 16.

69. Similarly surprising results also occurred in another clinical trial (JUMBO)-TIMI 26 Trial reported in Wiviott et al., "Randomized Comparison of Prasugrel (CS-747, LY640315) a Novel Thienopyridine P2Y12 Antagonist, With Clopidogrel in Percutaneous Coronary Intervention: Results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 Trial" Circulation, 111, 3366-3373 (2005)(Exhibit 29) relating to administration of different doses of prasugrel in combination with aspirin as compared to clopidogrel and aspirin. The paper reports that "[b]leeding rates for all treatment groups [of prasugrel and aspirin] were **lower than expected** for clopidogrel plus aspirin from prior PCI trials." Id. at 3370 (emphasis added).

70. In fact, I had expressed surprise in 2009 in commenting on the results from the TRITON-TIMI 38 study showing that in STEMI patients, prasugrel reduced ischemic events compared to clopidogrel without a significant increase in bleeding risks. In O'Riordan, "Prasugrel bests clopidogrel without bleeding risk in STEMI subgroup in TRITON-TIMI 38, researchers say," Heartwire (March 5, 2009)(Exhibit 30) my comments were summarized:

> Regarding the lack of bleeding risk observed in STEMI patients, he [Dr. Paul Gurbel] said the results "are not what you'd expect" considering the amount of GPIIb/IIIa inhibitor used. Also, he noted that the rate of non-CABG TIMI major bleeding was greater in STEMI patients than in the overall cohort -- up from 1.8% to 2.1% in the STEMI cohort -- but was unchanged with prasugrel, another finding that is unexpected, given that prasugrel is a more potent antiplatelet agent.

Thus, in 2009, I had expected that prasugrel with aspirin would increase bleeding in these patients more than it actually did.

Opinion F: The combination of prasugrel and aspirin surprisingly addresses interpatient variability of response to clopidogrel and aspirin, which could not have been expected by one skilled in the art as of December 25, 2000

71. It is my opinion that the combination of prasugrel and aspirin surprisingly addresses interpatient variability of response to clopidogrel and aspirin, which could not have been expected by one skilled in the art as of December 25, 2000. The basis of my opinion is detailed below.

72. As of the priority date of the '168 application, it was recognized that a significant portion of the patient population does not respond to the anti-platelet aggregation effects of thienopyridines, namely ticlopidine and clopidogrel, as well as aspirin, resulting in adverse clinical outcomes. The cause of this interpatient variability was not known at that time. It was not known, and could not have been predicted, as of the priority date of the '168 application, that

patients would exhibit considerably less variability in responsiveness to the combination of prasugrel and aspirin. Regardless of whether the increased consistency of response was due to the properties of prasugrel or the combination of prasugrel plus aspirin, as of December 25, 2000, one could not have predicted that the combination of aspirin and prasugrel would result in a more consistent response than the combination of clopidogrel and aspirin.

73. The interpatient variability of response to each of clopidogrel and aspirin was reported prior to the filing date of the present application in Van De Graaff et al., "Variable Interindividual Responses to Antiplatelet Therapies- Do They Exist, Can We Measure Them, and Are They Clinically Relevant?" Heart Drug, 1(1):35-43 (2001)("Van De Graaff")(Exhibit 31), which was made available online as of August 2000. With respect to aspirin, Van De Graaff describes that "platelet function studies reveal a significant variation in an individual's response to aspirin and suggest that a subset of the population might be resistant to the drug's protective effects against thromboembolic complications." Id. at 39. For example, Van De Graaff reported in a clinical trial assessing long-term cardiovascular events that "8-12% of patients taking aspirin do not achieve the therapeutic benefit of platelet inhibition, based on aggregometry." Id. Van De Graaff also reported substantial variation in aggregation response to ADP for ticlopidine and clopidogrel. For example, Van De Graaff reports that "15% of specimens revealed increased aggregation with ticlopidine" and that clopidogrel demonstrated a large range of variability, ±27% from the mean." See Id. In view of this data, Van de Graaff reported that "[a]lthough not as well studied as with aspirin, interindividual variability has also been observed in platelet reactivity during treatment with this class of medication," referring to the class of thienopyridines. Id. By specifically referring to the class of thienopyridines as being associated with interindividual variability, Van de Graaff provides a reasonable expectation that prasugrel,

another thienopyridine, would behave similarly, not differently, from other thienopyridines, and thus would not be useful to treat individuals who are unresponsive to clopidogrel.

74. The interpatient variability discussed in Van de Graaff is further supported by Farrell et al., "The Lack of Augmentation by Aspirin of Inhibition of Platelet Reactivity by Ticlopidine," Am J Cardiol., 83; 770-774 (1999)(Exhibit 32), which reported marked interindividual variability in platelet reactivity in response to ticlopidine alone and to a combination of ticlopidine and aspirin.

75. With respect to clopidogrel, a figure submitted to the Food and Drug Administration (FDA) for the approval of PLAVIX, reproduced below:

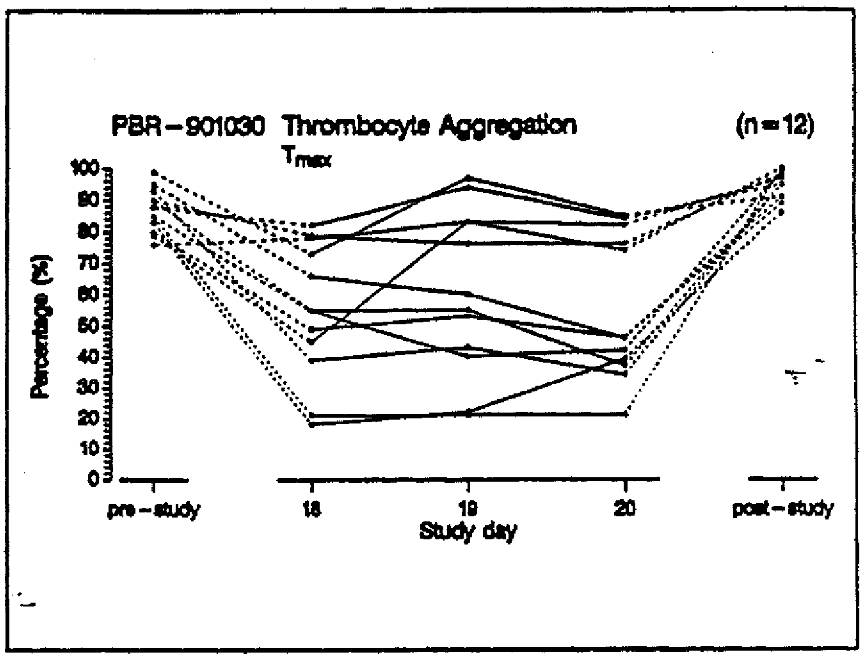


Figure 2. **Individual ADP induced thrombocyte aggregation (T_{max}) versus time profiles during multiple oral administration of 0.25 mg of digoxin daily from day 1 through day 20**
Days 1-10 = without clopidogrel
Days 11-20 = during 75 mg clopidogrel daily from day 10 through day 20

shows that patients administered clopidogrel showed great interindividual variation in ADP induced thrombocyte aggregation. As shown by two peer reviewed publications, the interpatient variability of response to clopidogrel was recognized by scientists as early as 1999. See Schwarz et al., "Flow Cytometry Analysis of Intracellular VASP Phosphorylation for the Assessment of Activating and Inhibitory Signal Transduction Pathways in Human Platelets, Definition and Detection of Ticlopidine / Clopidogrel Effects," Thromb. Haemost, 82: 1145-52 (1999)(Exhibit 33); and Geiger et al., "Specific Impairment of Human P2YAC ADP Recptor-Mediated Signaling by the Antiplatelet Drug Clopidogrel," Arterioscler. Thromb. Vasc. Biol., 19: 2007-2011 (1999)(Exhibit 34).

76. The variability in response reported earlier by Van de Graaff has continued to be confirmed for combinations of clopidogrel and aspirin. In fact, my colleagues and I published a study providing evidence of interpatient response variability and drug resistance to the combination of clopidogrel and aspirin in Gurbel et al., "Clopidogrel for Coronary Stenting: Response Variability, Drug Resistance, and the Effect of Pretreatment Platelet Reactivity," Circulation 107:2908-2913 (2003)(Exhibit 35). At that time, the underlying basis for the response variability was not known.

77. The variable response to treatment with clopidogrel and aspirin leaves a subpopulation of patients subject to continued risk for cardiovascular events creating an unmet need, unexpectedly met by prasugrel and aspirin. For example, the European Medicines Agency (EMEA) report notes that "it has been shown that 'non-responsiveness' to a clopidogrel 600 mg LD is a strong predictor of stent thrombosis in patients receiving drug-eluting stents, and in addition, that residual platelet aggregation above the median is associated with a 6.7-fold increased risk of major cardiac events (death, myocardial infarction and target vessel

revascularisation) at 1 month follow-up in patients undergoing elective PCI." EMEA Assessment Report for Efient, Doc. Ref. EMEA/117561/2009 at page 4 ("EMEA Report")(Exhibit 36). Moreover, the variable response to treatment with clopidogrel and its use in combination with aspirin has been recognized in "[a] growing number of studies [that] have linked poor antiplatelet response to clopidogrel to adverse clinical outcomes, particularly coronary ischemia and stent thrombosis." Wiviott et al., "Prasugrel," Circulation, 122: 394-403 (2010)("Wiviott Review")(Exhibit 37).

78. It has been found that one possible explanation for the differences in the interpatient variability of clopidogrel in combination with aspirin as compared prasugrel in combination with aspirin is the inability of certain patients to metabolize clopidogrel, which is a prodrug, into its active form. The Wiviott Review reports that, "[t]he CYP enzymes involved in [the] conversions [of prasugrel and clopidogrel into their active forms] are known to be subject to common genetic variation resulting in differential function." Id. at 399. As summarized by the Wiviott Review, "several studies have reported that patients who are carriers of a reduced-function allele of CYP 2C19 are at increased risk of recurrent cardiovascular events, including MI and stent thrombosis, while being treated with clopidogrel." Id. In particular, the Wiviott Review reports that "[a]mong the clopidiogrel subjects, carriers had an excess of cardiovascular ischemic events, including a 3-fold higher rate of stent thrombosis. Id. at 399.

79. Subsequent studies have demonstrated that administration of the combination of prasugrel and aspirin results in more consistent anti-platelet activity across the patient population. A study based on a large scale clinical study, TRITON-TIMI 38 Trial, reported in Mega et al., "Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidiogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic

analysis," Lancet (Published online August 29, 2010)("Mega")(Exhibit 38), provides clinical evidence that the population found resistant to clopidogrel and aspirin was indeed susceptible to treatment with prasugrel and aspirin. As reported in Mega:

> …none of the common variants in the CYP genes tested showed consistent reductions in prasugrel active metabolite generation and the antiplatelet effects of prasugrel. Consequently, subjects assigned to prasugrel in the TRITON-TIMI 38 genetic analysis had no difference in the rates of cardiovascular ischemic events by genotype· suggesting that the more efficient metabolism of prasugrel may render patients less susceptible to such genetic variation. Id. at 1.

80. In view of these significant health risks associated with non-responsiveness to clopidogrel and aspirin, the FDA modified the prescribing information for PLAVIX, the commercially sold drug product that contains the active ingredient clopidogrel, with a black box warning that recommends consideration of alternative treatment or treatment strategies. See PLAVIX label. In response to the black box warning for PLAVIX and recognizing the difficulties clinicians face when dealing with interpatient variability, one of the options recommended by the authors in Roden et al. "Responding to the Clopidogrel Warning by the US Food and Drug Administration: Real Life Is Complicated," Circulation, 122: 445-448 (2010)(Exhibit 39) is to ignore clopidogrel and prescribe prasugrel, which further evidences the unexpected ability of prasugrel in combination with aspirin to fill an unmet need. See Id. at 446.

81. Based upon what was known at the priority date, it was unexpected that the combination of prasugrel and aspirin would overcome this genetic variation and address the problem of non-responders to the combination of clopidiogrel and aspirin.

Opinion G: The combination of prasugrel and aspirin provides unexpectedly superior results as compared to the combination of clopidogrel and aspirin in patients with diabetes mellitus

82. It is my opinion that the combination of prasugrel and aspirin provides unexpectedly superior results as compared to the combination of clopidogrel and aspirin in patients with diabetes mellitus. The basis for this opinion is detailed below.

83. The clinical benefits of prasugrel in combination with aspirin are generally and unexpectedly even more pronounced in patients having diabetes mellitus (DM). For example, in a separate paper by the clinicians for the TRITON-TIMI 38 trial, Wiviott et al., "Greater Clinical Benefit of More Intensive Oral Antiplatelet Therapy With Prasugrel in Patients with Diabetes Mellitus in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel -- Thrombolysis in Myocardial Infarction 38," Circulation, 118, 1626-1636 (2008)("2008 Wiviott")(Exhibit 40), it was reported that "[a]lthough key ischemic end points, including the primary end point and MI, were significantly reduced among subjects both with and without DM, a greater relative reduction was seen in favor of **prasugrel [in combination with aspirin] among subjects with DM**...." Id. at 1630 (emphasis added). Specific data showing that prasugrel in combination with aspirin provides a greater benefit than clopidogrel with aspirin in most DM patients were reported in Table 4, which is reproduced below:

Table 4. Clinical Events for Prasugrel Versus Clopidogrel by Diabetes Status

	Clopidogrel, %	Prasugrel, %	HR (95% CI)	P	$P_{interaction}$ vs No Diabetes
Subjects without DM (n=10 462), n	5225	5237			
CVD/MI/CVA*	10.6	9.2	0.86 (0.76–0.98)	0.02	
CVD/MI*	10.0	8.5	0.85 (0.75–0.97)	0.01	
MI†	8.7	7.2	0.82 (0.72–0.95)	0.006	
CV death	1.9	1.7	0.91 (0.68–1.23)	0.53	
Stent thrombosis	2.0	0.9	0.45 (0.31–0.65)	<0.001	
Major hemorrhage‡	1.6	2.4	1.43 (1.07–1.91)	0.02	
Major or minor‡	3.6	4.9	1.32 (1.08–1.61)	0.006	
D/MI/CVA*/major bleed‡	12.3	11.5	0.92 (0.82–1.03)	0.16	
All diabetes (n=3146), n	1570	1576			
CVD/MI/CVA*	17.0	12.2	0.70 (0.58–0.85)	<0.001	0.09
CVD/MI*	15.4	10.8	0.68 (0.56–0.84)	<0.001	0.08
MI†	13.2	8.2	0.60 (0.48–0.76)	<0.001	0.02
CV death	4.2	3.4	0.85 (0.58–1.24)	0.40	0.78
Stent thrombosis	3.6	2.0	0.52 (0.33–0.84)	0.007	0.63
Major hemorrhage‡	2.6	2.5	1.06 (0.66–1.69)	0.81	0.29
Major or minor‡	4.3	5.3	1.30 (0.92–1.82)	0.13	0.93
D/MI/CVA*/major bleed‡	19.2	14.6	0.74 (0.62–0.89)	0.001	0.05

Abbreviations as in Table 2.
*The composite of cardiovascular death and nonfatal end points (MI alone or MI/stroke).
†Any MI (fatal or nonfatal).
‡Not related to CABG.

In view of this data, the paper reports that:

- a ***<u>14%</u> overall reduction*** in the primary end point was seen with prasugrel in combination with aspirin as compared to clopidiogrel with aspirin in subjects ***without DM*** and a **<u>30%</u> reduction** in the primary end point in **subjects with DM;**
- a ***<u>18%</u> overall reduction*** in MI was seen with prasugrel in combination with aspirin as compared to clopidiogrel with aspirin in subjects ***without DM*** and a **<u>40%</u> reduction** in MI in **subjects with DM;**
- a ***<u>55%</u> overall reduction*** in stent thrombosis was seen with prasugrel in combination with aspirin as compared to clopidiogrel with aspirin in subjects ***without DM*** and a **<u>48%</u> reduction** in stent thrombosis in **subjects with DM.** <u>Id.</u> at 1628-1629.

The paper recognizes that the increased benefit of prasugrel in combination with aspirin in DM patients ***could not have been predicted*** by the effects of dual antiplatelet therapy with aspirin and

clopidogrel because "in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial of subjects with ACS, dual antiplatelet therapy with aspirin and clopidiogrel was associated with a similar benefit regardless of DM, although event rates were higher among subjects with DM." Id. at 1633.

84. Thus, again, the combination of prasugrel and aspirin provides an unexpected result in an enhanced benefit to a population of patients that had not previously demonstrated a distinction when treated with clopidogrel and aspirin. Such results further support the non-obviousness of the claimed invention.

85. I further declare that all statements made herein are of my own knowledge, and are believed true, and further that these statements were made with the knowledge that the willful false statements, and the like so made punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, or any patent issuing thereon.

Date: October 13, 2011

Paul A. Gurbel, M.D.

LIST OF EXHIBITS
FOR
AFFIDAVIT OF PAUL A. GURBEL, M.D.

Exhibit 1: U.S. Patent Application Publication No. 2007/0010499

Exhibit 2: U.S. Patent No. 5,989,578

Exhibit 3: Asai et al., "CS-747, a New Platelet ADP Receptor Antagonist," Annu. Rep. Sankyo Res. Lab., 51: 1-44 (1999)

Exhibit 4: U.S. Patent No. 5,288,726

Exhibit 5: Gurbel et al., "Platelet Reactivity in Patients and Recurrent Events Post-Stenting: Results of the PREPARE POST-STENDING Study," J. Am. Coll. of Cardiol., 46:1820-1826 (2005)

Exhibit 6: Bonello et al., "Census and Future Direction on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate," J. Am. Coll. of Cardiol., 56:919-933 (2010)

Exhibit 7: Curriculum Vitae for Paul A. Gurbel, M.D.

Exhibit 8: Braunwald et al., "ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarcation: Executive Summary and Recommendations: Executive Summary and Recommendations, A Report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina)," Circulation, 102:1193-1209 (2000)

Exhibit 9: Smith et al., "ACC/AHA Guidelines for Percutaneous Coronary Intervention (Revision of the 1993 PTCA Guidelines) -- Executive Summary: A Report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty) Endorsed by the Society for Cardiac Angiography and Interventions," Circulation, 103:3019-3041 (2001)

Exhibit 10: Smith et al., "AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology," J. Am. Coll. Cardiol., 38: 1581-1583 (2001)

Exhibit 11: Vane et al., "Cyclooxygenases 1 and 2," Annu. Rev. Pharmacol. Toxicol., 38:97-120 (1998)

Exhibit 12: Awtry and Loscalzo, "Aspirin," Circulation, 101: 1206-1218 (2000)

Exhibit 13: Moussa et al., "Effectiveness of Clopdiogrel and Aspirin Versus Ticlopidine and Aspirin in Preventing Stent Thrombosis After Coronary Stent Implantation," Circulation, 99:2364-2366 (1999)

Exhibit 14: CAPRIE Steering Committee, "A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE)," Lancet, 348: 1329-39 (1996)

Exhibit 15: Package Insert for PLAVIX dated November 17, 1997

Exhibit 16: European Public Assessment Report (EPAR) report for PLAVIX dated October 2000

Exhibit 17: Leon et al., "A Clinical Trial Comparing Three Antithrombotic-Drug Regiments After Coronary-Artery Stenting," N. Engl. J. Med., 339: 1665-71 (1998)

Exhibit 18: Bertrand et al., "Double-Blind Study of the Safety of Clopidogrel With and Without a Loading Dose in Combination With Aspirin Compared with Ticlopidine in Combination With Aspirin After Coronary Stenting: The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)," Circulation, 102: 624-629, 625 (2000)

Exhibit 19: CURE Study Investigator, "The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme, rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease," European Heart Journal, 21: 2033-2041, 2034 (2000)

Exhibit 20: "The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigator: Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation," N. Engl. J. Med., 345(7) 494-502 (August 16, 2001)

Exhibit 21: Sugidachi et al., "The *in vivo* pharmacological profile of CS-747, a novel antiplatelet agents with platelet ADP receptor antagonist properties," British Journal of Pharmacology, 129: 1439-1446 (2000)

Exhibit 22: Storey, "The central role of the P_{2T} receptor in amplification of human platelet activation, aggregation, secretion and procoagulant activity," Brit. J. Haem. 110:925-934 (2000)

Exhibit 23: Paul et al., "Molecular Mechanism of Thromboxane A_2-induced Platelet Aggregation: Essential Role for $P2T_{AC}$ and α_{2A} Receptors," J. Biol. Chem. 274:29108-29114 (1999)

Exhibit 24: Verstraete, M., *et al.* (Eds.) Cardiovascular Thrombosis: Thrombocardiology and Thromboneurology, Lippincott Williams and Wilkins, Second Edition, 1998, Chapters 9-11, 14

Exhibit 25: Ferguson III, JA, *et al.* (Eds.) Antiplatelet Therapy in Clinical Practice, Martin Dunitz Press, 2000, Chapters 6 and 8-11

Exhibit 26: Wiviott et al., "Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes," N. Engl. J. Med., 357:20, 2001-15 (2007)

Exhibit 27: Smith et al., "Mortality Benefit with Prasugrel in TRITON-TIMI 38 Coronary Artery Bypass Grafting (CABG) Cohort: Risk Adjusted Retrospective Data Analysis," Circulation 122, A10881 (2010)

Exhibit 28: Bhatt et al., "Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events," N. Engl. J. Med., 354: 1706-17 (2006)

Exhibit 29: Wiviott et al., "Randomized Comparison of Prasugrel (CS-747, LY640315) a Novel Thienopyridine P2Y12 Antagonist, With Clopidogrel in Percutaneous Coronary Intervention: Results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 Trial" Circulation, 111, 3366-3373 (2005)

Exhibit 30: O'Riordan, "Prasugrel bests clopidogrel without bleeding risk in STEMI subgroup in TRITON-TIMI 38, researchers say," Heartwire (March 5, 2009)

Exhibit 31: Van De Graaff et al., "Variable Interindividual Responses to Antiplatelet Therapies- Do They Exist, Can We Measure Them, and Are They Clinically Relevant?" Heart Drug, 1(1):35-43 (2001)

Exhibit 32: Farrell et al., "The Lack of Augmentation by Aspirin of Inhibition of Platelet Reactivity by Ticlopidine," Am J Cardiol., 83; 770-774 (1999)

Exhibit 33: Schwarz et al., "Flow Cytometry Analysis of Intracellular VASP Phosphorylation for the Assessment of Activating and Inhibitory Signal Transduction Pathways in Human Platelets, Definition and Detection of Ticlopidine / Clopidogrel Effects," Thromb. Haemost, 82: 1145-52 (1999)

Exhibit 34: Geiger et al., "Specific Impairment of Human P2YAC ADP Recptor-Mediated Signaling by the Antiplatelet Drug Clopidogrel," Arterioscler. Thromb. Vasc. Biol., 19: 2007-2011 (1999)

Exhibit 35: Gurbel et al., "Clopidogrel for Coronary Stenting: Response Variability, Drug Resistance, and the Effect of Pretreatment Platelet Reactivity," Circulation 107:2908-2913 (2003)

Exhibit 36: EMEA Assessment Report for Efient, Doc. Ref. EMEA/117561/2009

Exhibit 37: Wiviott et al., "Prasugrel," Circulation, 122: 394-403 (2010)

Exhibit 38: Mega et al., "Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidiogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis," Lancet (Published online August 29, 2010)

Exhibit 39: Roden et al. "Responding to the Clopidogrel Warning by the US Food and Drug Administration: Real Life Is Complicated," Circulation, 122: 445-448 (2010)

Exhibit 40: Wiviott et al., "Greater Clinical Benefit of More Intensive Oral Antiplatelet Therapy With Prasugrel in Patients with Diabetes Mellitus in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel -- Thrombolysis in Myocardial Infarction 38," Circulation, 118, 1626-1636 (2008).